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Identical Male Twins with Congenital Adrenal Hyperplasia

Comparison of Growth, Serum and Urinary Steroids

MATTHEW H. CONNORS, MD
BAGHER M. SHEIKHOLISLAM, MD
Davis, California

THE SALT-LOSING form of congenital adrenal hyperplasia (CAH) results from an inborn error of steroid metabolism that is genetically determined and autosomal recessive.[1] It is known to occur in siblings but to our knowledge there is only one report of this form of the condition reported in identical twins.[2] The effect of the 21-hydroxylase enzyme deficiency in some patients is a lack of cortisol and mineralocorticoid biosynthesis. There is increased adrencorticotropin (ACTH) secretion because of the cortisol deficiency and this can be largely suppressed by exogenous glucocorticoids. Therapy is aimed at suppression of excess ACTH by physiological amounts of glucorticoids to prevent virilization and rapid skeletal maturation. Discontinuation of therapy usually results in a prompt increase in adrenal androgen secretion. The cortisol replacement therapy is adjusted on the basis of the growth pattern and the urinary steroid concentrations. Growth retardation has still resulted in some patients despite application of these principles of therapy. This paper reports the first cases of CAH in identical male twins, which afforded us the opportunity to compare adrenal function as well as growth rates on varying glucocorticoid replacement regimens. The usefulness of plasma 17-hydroxyprogesterone (17-OHP) levels for the diagnosis of CAH and the therapeutic management is compared with the measurement of urinary steroid metabolites.

From the Department of Pediatrics, University of California, Davis, School of Medicine.

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Reprint requests to: Matthew H. Connors, MD, Department of Pediatrics, University of California, Davis, School of Medicine, Davis, CA 95616.

ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropin
CAH = congenital adrenal hyperplasia
17-OHP = 17-hydroxyprogesterone
DOC = desoxycorticosterone
GH = growth hormone

Report of Cases

The babies were born after an uneventful 36-week pregnancy. The delivery was normal. The parents are not related and there is no family history of genital abnormalities or deaths in the neonatal period. There are two healthy siblings. The first twin G.S. weighed 4 pounds 11 oz at birth and the second D.S. weighed 4 pounds 7 oz. The placenta and amniotic membranes were not examined. Findings on physical examination were within normal limits and the twins looked alike. Major and minor blood groups were identical. Both twins required oxygen during the initial 48 hours of life because of respiratory distress. At five days of age both twins began regurgitating all feedings and losing weight. D.S. became severely dehydrated and had an episode of respiratory arrest at eight days of age. Serum electrolyte concentrations on the eighth day of life were: for D.S., sodium 126 mEq per liter, potassium 11.3 mEq per liter; for G.S., sodium 121 mEq per liter, potassium 12.1 mEq per liter. Resuscitation was successful and was followed by intravenous infusion of normal saline and hydrocortisone sodium succinate (Solu-Cortef®). Administration of desoxycorticosterone (DOC) acetate, 2 mg per day, was begun by the private physician.

The conditions of infants improved, and at 11 days of age they were transferred to the University of California, Davis-Sacramento Medical Center. A regimen of dexamethasone, 0.9 mg divided into four doses per day, was begun and 24-hour urine specimens were obtained which showed on analysis negligible amounts of 17-ketosteroids and pregnanetriol excretions of 0.1 and 0.3 mg per 24 hours (Table 1). At 12 days of age baseline plasma 17-OHP concentrations, determined by radioimmunoassay method[3] were low in D.S. and elevated in G.S., but in both infants there were abnormally high values 30 minutes after the intramuscular administration of

TABLE 1.—*Effect of Glucocorticoid Therapy on Steroid Metabolites in Identical Male Twins (G.S. and D.S.)*

		Urinary (mg/24 hours)				*Plasma 17-OHP (ng/ml)*			
		17-ketosteroid		*Pregnanetriol*		*Baseline*		*Adrenal Stimulation**	
Age	*Treatment*	*G.S.*	*D.S.*	*G.S.*	*D.S.*	*G.S.*	*D.S.*	*G.S.*	*D.S.*
12 days	0.9 mg dexamethasone during 24 hours	0.5	0.7	0.1	0.3	6.13	0.63	8.3	8.3
2 months	2 days after 25 mg cortisone acetate	..	..	1.7	3.5	..	..	..	..
4 months	2 days after 25 mg cortisone acetate	..	..	0.2	..	..	..	..	..
11 months	1 day after 25 mg cortisone acetate	0.6	0.9	0.4	0.5	1.26	4.28	..	..
	2 days after 25 mg cortisone acetate	0.5	1.0	0.5	0.4	1.24	1.24	..	..
	3 days after 25 mg cortisone acetate	0.7	0.6	0.2	..	4.94	4.06	7.21	8.28
16 months	Oral cortisol 10 mg	1.7	1.7	0.4	0.3	..	..	..	..
17 months	Oral cortisol 5 mg	1.3	1.0	1.0	0.6	..	..	..	..
18 months	Oral cortisol 5 mg	1.3	1.0	0.9	1.2	..	..	..	..
	No cortisol × 5 days, daily stimulation*	1.0	1.3	1.1	0.7	..	..	13.7	..
21 months	No cortisol × 5 days	1.7	3.0	6.4	8.8	..	..	..	..

*0.25 mg α 1-24 corticotropin (Cortrosyn®) given intramuscularly; plasma for 17-hydroxyprogesterone (17-OHP) obtained after 30 minutes.

Cortrosyn® (α 1-24 corticotropin). Attempts to gradually reduce the daily DOC acetate administration resulted in urinary sodium loss and increased serum potassium concentrations indicating mineralocorticoid deficiency. Conditions of the twins were stable on a regimen of 25 mg of cortisone acetate given intramuscularly every three days, 1 mg of DOC acetate per day and orally given sodium chloride supplementation. Intravenous pyelograms were interpreted as normal at one month of age with no evidence of adrenal calcification in either patient. At 45 days of age they weighed 5 pounds and were discharged on a regimen of 25 mg of cortisone acetate given intramuscularly every third day, 18.75 mg of DOC trimethylacetate per month and 2 gm of salt daily as a supplement to dietary sodium. The diagnosis at discharge was adrenal insufficiency due to adrenal 21-hydroxylase deficiency.

Vomiting and irritability developed 23 days after the injection of DOC-trimethylacetate and the children were admitted to hospital. The serum electrolyte concentrations were: for G.S., sodium 130 mEq per liter, potassium 8.5 mEq per liter; for D.S., sodium 127 mEq per liter, potassium 10.1 mEq per liter. At this time 24-hour urine specimens showed 1.7 mg of pregnanetriol for G.S. and 3.5 mg for D.S. These values were obtained two days after the last dose of cortisone acetate. Because of these findings the dose of DOC-trimethylacetate was increased to 25 mg per month. The twins did not do well over the next nine months, with repeated episodes of vomiting and irritability occurring 24 to 27 days after each injection of DOC-trimethylacetate. Collections of 24-hour urine specimens repeatedly showed negligible changes in 17-ketosteroid and pregnanetriol levels (Table 1). When the infants were 11 months old, plasma concentrations of 17-OHP were determined at 8 AM on three consecutive days following administration of 25 mg of cortisone acetate (Table 1). Daily fluctuation of 17-OHP levels in the abnormal range was found despite the low urinary excretion of steroids. On the third day after receiving cortisone acetate, 0.25 mg of Cortrosyn was given intramuscularly to each patient at 8 AM and further elevations of the plasma 17-OHP concentrations were found after 30 minutes. At 11 months of age two 125 mg DOC acetate pellets were implanted in each child, and oral administration of cortisol was begun in a dosage of 5 mg three times a day; irritability did not recur.

The growth of the twins continued to be poor (Figure 1) and therefore the total cortisol dosage was decreased to 10 mg per day at 16 months and 5 mg per day at 17 months of age. Despite these reductions there were only slight increases in the urinary levels of 17-ketosteroids and pregnanetriol (Table 1). At 18 months of age the cortisol was discontinued and 0.25 mg of Cortrosyn was administered intramuscularly for five consecutive days in order to determine whether the adrenal hypoactivity was reversible. Urine specimen collections begun on the fifth day showed no measurable increase in 17-hydroxysteroids, 17-ketosteroids or pregnanetriol levels. In contrast, however, the plasma 17-OHP concentration in G.S. at the end of this period had reached a level of 13.7 ng per ml.

The twins' rate of growth now began to increase while being given 5 mg per day of cortisol.

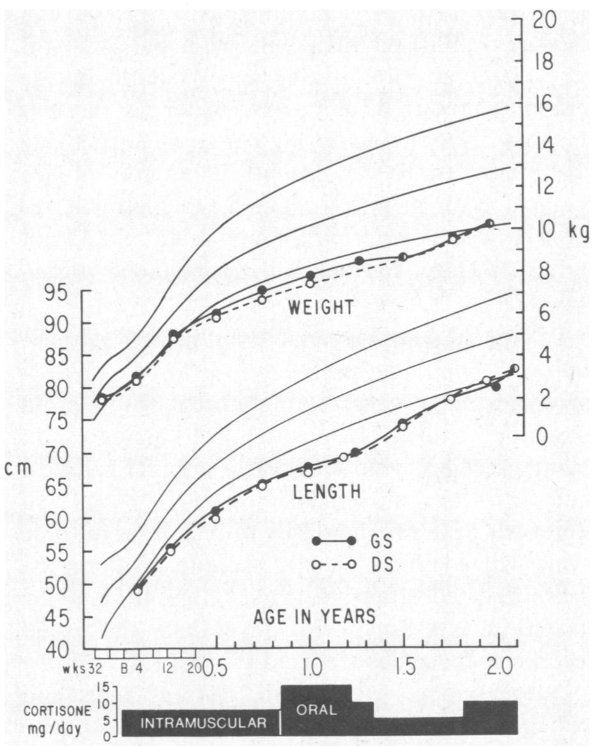

Figure 1.—Comparison of growth of identical male twins (G.S. and D.S.) corrected for gestational age and glucocorticoid dosage. Growth lines represent 2 SD and mean. Chart modified after Tanner.

At 21½ months the administration of cortisol was again discontinued for five days and urine specimens collected at the end of that period. The levels of 17-ketosteroids and pregnanetriol were now abnormally elevated, indicating the return of endogenous adrenal activity.

At 22 months of age both twins began to exhibit irritability and were found to be hyperkalemic and hyponatremic. Administration of 0.1 mg per day of 9α-fluoro-hydrocortisone (Florinef®) was started along with 10 mg per day of cortisol (given orally, half the dose in the morning). They have done well on this replacement regimen.

Discussion

Congenital adrenal hyperplasia resulting from 21-hydroxylase deficiency is not clinically apparent in newborn male infants. In the absence of a positive family history the condition may remain unrecognized until severe dehydration and salt depletion develop. These crises may not occur until after the newborn has gone home from the nursery and thus the cause of death may not be known. Most female infants born with this disorder are usually diagnosed at birth due to apparent virilization. This difficulty in diagnosing the salt losing type of CAH in males probably accounts for the preponderance of females with this disorder in some clinics. Early treatment begun with cortisone and DOC acetate because of the electrolyte abnormalities found during the salt losing crises can be lifesaving but can also delay a definitive diagnosis. These events occurred in the identical male twins described in this report. The dehydration and the salt loss were remarkably similar in timing and severity. Because of their small size and unstable condition we attempted to make the diagnosis of CAH without the discontinuation of steroid therapy. An equivalent amount of dexamethasone was substituted for their cortisone in order to reduce interference with the measurement of endogenous urinary steroid metabolites. The negligible amount of urinary steroid measured was not diagnostic of CAH. Plasma 17-OHP determinations were obtained in order to differentiate CAH from complete adrenal insufficiency.

In normal infants up to six weeks of age, the mean value for plasma 17-OHP is 2.1 ng per ml.[4] In three normal patients stimulated with ACTH, the plasma concentration of 17-OHP ranged from 2.4 to 4.8 ng per ml.[5] Values in most untreated patients with CAH range from 1 to 40 ng per ml.[4] Franks found slightly higher values of plasma 17-OHP in untreated patients with the salt-losing form of CAH.[5] Therefore, plasma concentrations of 17-OHP are usually much higher in untreated patients with CAH than in normal subjects, even normal subjects treated with ACTH. After treatment of CAH with glucocorticoids, the 17-OHP concentration decreases notably and may become normal.[4-6] Utilizing a competitive protein binding method for measurement of 17-OHP, Barnes and Atherden showed there to be an increase after adrenal stimulation in the plasma 17-OHP concentration of children with CAH who were treated with suppressive doses of cortisone.[6] No detectable increase after adrenal stimulation was found in normal children.

In the identical twins in this report resting plasma 17-OHP levels were found to be elevated in only one after the first four days of glucocorticoid therapy. Both twins had an increase in plasma 17-OHP concentration after adrenal stimulation and this along with the salt-losing tendency confirmed the diagnosis of a 21-hydroxylase defect of the adrenal. The genetic expression of the adrenal enzymatic defect was much the same in both twins, as indicated by the comparable pattern of urinary steroid excretion during therapy. The chief urinary metabolite of 17-OHP is pregnanetriol. While periodic measurements of plasma 17-OHP during therapy showed abnormal concentrations, the urinary pregnanetriol as well as 17-ketosteroid amounts were normal on many occasions. This may be explained in part by the DOC acetate which the twins were receiving. The radioimmunoassay method used to measure 17-OHP also measures DOC with the percent cross-reactivity being 35 percent.[3] This interference, however, would not account for the rapid rise in 17-OHP measured in the plasma 30 minutes after adrenal stimulation. Therefore, measurement of the plasma 17-OHP concentration is of value in the diagnosis of the 21-hydroxylase deficiency form of CAH but as a guide to therapy it may be too sensitive an index of adrenal activity.

In the twins at first there was evidence of subnormal linear growth as well as delayed skeletal maturation which could be due to the steroid they received. Intramuscular injections of 25 mg of cortisone acetate were given every third day as has been recommended for the first year of life.[7] The adrenal hypoactivity and growth retardation which ensued suggest that this dose of glucocorticoid was excessive. The normal cortisol production rate has been determined to be 12.1 ± 2.9 mg per sq meter per day from the age of four months to 20 years.[8] The dose of steroid the twins received represented 20 to 30 mg per sq meter per day during the first year of life. Raiti and Newns[9] found that eight of 35 children with the salt-losing form of CAH who received oral cortisone doses in excess of 36 mg per sq meter per day failed to grow satisfactorily. The intramuscular glucocorticoid dosage used in our patients was well below this limit during the first year of life and still growth was poor. Although cortisone acetate injections every third day have not been shown to suppress growth hormone (GH) release in subjects with CAH,[8,10] the continuous blood level of cortisol maintained under these conditions may interfere with peripheral GH action. Rudman and associates[11] have shown that cortisol given near the time of GH administration diminishes the peripheral anabolic actions of GH. The daily oral dose of cortisol usually recommended is twice the cortisol production rate.[12] In these patients oral cortisol therapy was started at 11 months of age and amounted to 37 mg per sq meter per day but this was decreased to 10 mg per sq meter per day at 17 months. It was around 18 months of age that catch-up growth occurred. The growth retarding effects of steroid therapy seem related not only to dosage, but also to the hormone preparation.[13]

It appears from our analysis of growth in these identical twins that relatively low doses of glucocorticoids were required to suppress both steroid excretion and growth. Identical increases in growth rate occurred along with adrenal suppression with the oral cortisol dose of 10 mg per sq meter per day. The similarity of responses in these twins with identical genetic makeup supports the concept that certain patients with CAH may be treated successfully with less than the usual recommended glucocorticoid therapy. In contrast to measurements of plasma 17-OHP levels and urinary steroid metabolites the linear growth rate of these patients was found most reliable in the therapeutic management.

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